The utility of impulsive bias and altered decision-making as predictors of drug efficacy and target selection: Rethinking behavioral screening for antidepressant drugs

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Non-standard abbreviations:

5-choice serial reaction time test (5-CSRTT); 5,7-dihydroxytryptamine (5,7-DHT); amphetamine (1-phenylpropan-2-amine); aripiprazole (7-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy)-3,4-dihydro-2(1H)-quinolinone); atomoxetine ((3R)-N-methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine); attention deficit hyperactivity disorder (ADHD); bupropion (2-(tert-butylamino)-1-(3-chlorophenyl)propan-1-one); clenbuterol (1-(4-amino-3,5-dichlorophenyl)-2-(tert-butylamino)ethanol); desipramine (3-(5,6-dihydrobenzo[b][1]benzazepin-11-yl)-N-methylpropan-1-amine); differential-reinforcement-of-low rate 72-s schedule (DRL 72-s); dizocilpine or [5R,10S]-[+]-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801); dopamine transporter (DAT); dorsal anterior cingulate cortex (dACC); eticlopride (5-chloro-3-ethyl-N-[[2S]-1-ethylpyrrolidin-2-yl]methyl]-2-hydroxy-6-methoxybenzamide); fluoxetine (N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine); GBR12909 (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-
phenylpropyl)piperazine; dihydrochloride); guanfacine (N-(diaminomethylidene)-2-(2,6-dichlorophenyl)acetamide); imipramine (3-(5,6-dihydrobenzo[b][1]benzazepin-11-yl)-N,N-dimethylprop-1-amine); intralimbic cortex (IL); interresponse time (IRT); ketamine (2-(2-chlorophenyl)-2-(methylamino)cyclohexanone); ketanserin (3-[2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl]-1H-quinozoline-2,4-dione); M100907 ((R)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol); major depressive disorders (MDD); methylazoxymethanol acetate or MAM ((Z)-hydroxymethylimino-methyl-oxidoazanium); medial prefrontal cortex (mPFC); methylphenidate (methyl 2-phenyl-2-piperidin-2-ylacetate); muscimol (5-(aminomethyl)-1,2-oxazol-3-one); N-methyl-D-aspartate (NMDA); methylphenidate (methyl 2-phenyl-2-piperidin-2-ylacetate); nefazodone (2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-5-ethyl-4-(2-phenoxyethyl)-1,2,4-triazol-3-one); nomifensine (2-methyl-4-phenyl-3,4-dihydro-1H-isoquinolin-8-amine); norepinephrine transporter (NET); nortriptyline (3-(5,6-dihydridibenzo[2,1-b:2',1'-f][7]annulen-11-ylidene)-N-methylpropan-1-amine); olanzapine (2-methyl-4-(4-methylpiperazin-1-yl)-5H-thieno[3,2-c][1,5]benzodiazepine); (+)-oxaprotiline ((+)-3-(9,10-ethano-9,10-dihydro-9-anthryl)-1-methylamino-2-propanol); pilocarpine ((3S,4R)-3-ethyl-4-(3-methylimidazol-4-yl)methyl)oxolan-2-one); pipamperone (1-[4-(4-fluorophenyl)-4-oxobutyl]-4-piperidin-1-ylpiperidine-4-carboxamide); prazosin (2-[4-(5-aminooctahydroquinazolin-2-yl)piperazin-1-yl]-(fur-an-2-yl)methanone); prefrontal cortex (PFC); prelimbic cortex (PrL); quetiapine (2-[2-[4-benzol[b][1,4]benzothiazepin-6-yl)piperazin-1-yl]ethoxy]ethanol); quinpirole (4aR,8aR)-5-propyl-1,4,4a,6,7,8,8a,9-octahydropyrazolo[3,4-g]quinoline); R-CPP (3-((R)-2-Carboxypiperazin-4-yl)-propyl-1-phosphonic acid); reboxetine ((2S)-2-[(S)-(2-ethoxyphenoxy)-phenylmethyl]morpholine); risperdone (3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyridol[1,2-a]pyrimidin-4-one; serotonin-norepinephrine reuptake inhibitors (SNRIs); salbutamol (4-[2-(tert-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol); scopalamine (6,7 epoxytropine tropate); selective serotonin reuptake inhibitors (SSRIs); sertraline (1S,4S-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine); stop-signal reaction time task (SSRT); tricyclic antidepressants (TCAs); sulpiride (N-[(1-ethylpyrroloidin-2-yl)methyl]-2-methoxy-5-sulfamoylbenzamide); trazodone (2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-1,2,4-triazolo[4,3-a]pyridine-3-one); venlafaxine (1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol); (ventral hippocampus (VH).
ABSTRACT
Cognitive dysfunction may be a core feature of major depressive disorder (MDD) including affective processing bias, abnormal response to negative feedback, changes in decision making, and increased impulsivity. Accordingly, a translational medicine paradigm predicts clinical action of novel antidepressants by examining drug-induced changes in affective processing bias. With some exceptions, these concepts have not been systematically applied to preclinical models to test new chemical entities. The purpose of this review is to examine whether an empirically-derived behavioral screen for antidepressant drugs may screen for compounds, at least in part, by modulating an impulsive biasing of responding and altered decision-making. The differential-reinforcement-of low rate 72-s (DRL 72-s) schedule is an operant schedule with a documented fidelity for discriminating antidepressant drugs from non-antidepressant drugs. However, a theoretical basis for this empirical relationship has been lacking. Therefore, this review will discuss whether response bias towards impulsive behavior may be a critical screening characteristic of DRL behavior requiring long inter-response times to obtain rewards. This review will compare and contrast DRL behavior with the 5-choice serial reaction time test (5-CSRTT), a test specifically designed for assessing motoric impulsivity, with respect to psychopharmacological testing and the neural basis of distributed macrocircuit underlying these tasks. This comparison suggests that the existing empirical basis for the DRL 72-s schedule as a pharmacological screen for antidepressant drugs is complemented by a novel hypothesis that altering impulsive response bias for rodents trained on this operant schedule is a previously unrecognized theoretical cornerstone for this screening paradigm.
INTRODUCTION

Given the wealth of diverse symptoms characterizing major depressive illness, providing optimal translation from preclinical animal studies to experiments with healthy volunteers or dysthmic individuals to clinical antidepressant trials may require understanding the core features of major depressive episodes. Anhedonia, an inability to experience pleasure is one of the key symptoms of depression that has been used to model depression in animal studies. Another potential core symptom is hopelessness, a symptom related to poorly adaptive cognitive processing. In recent years cognitive dysfunction is increasingly recognized as being impaired in major depressive disorders (MDD). Given the heterogeneity of MDD, preclinical screening paradigms based on multiple core/key symptoms are warranted to provide optimal predictions toward testing in clinical populations, since it is unlikely that any single preclinical paradigm can adequately predict translation to positive and negative clinical trials.

The cognitive symptoms of mood disorders include hopelessness, feelings of worthlessness or inappropriate guilt, diminished ability to think or concentrate or indecisiveness, and recurrent thoughts of death and suicidal ideation/attempts. In the middle to late 1960’s, Aaron Beck described a negative triad for depressed patients including a negative interpretive bias towards oneself, the world and one’s future (Beck, 2008). Cognitive behavioral therapy was derived from this theoretical underpinning of ruminative cognitive misperceptions pervading the life of depressed patients and has been widely used in the treatment of depressed and/or anxious patients. Impulsiveness may be another expression of disturbed executive functions in patients with mood disorders; motoric impulsivity may interact with depression severity to moderate suicidal ideation in at least some depressed patients (Wang et al., 2015; Westheide et al., 2008).

This current review posits that one frequently used empirically-derived behavioral screen for antidepressant drugs may depend on improving cognition. After describing the clinical understanding for neurocognitive dysfunction in MDD, research directed at utilizing drug-induced changes in emotional
processing as a translational tool for predicting the clinical effects of drugs in randomized clinical trials (RCTs) will be outlined. This will then lead to a discussion of how altering impulsivity (action or motoric impulsivity) may be an underlying basis for the positive predictability of the differential-reinforcement-of-low rate 72-s (DRL 72-s) schedule with respect to antidepressant drug development. Specifically, the pharmacology and neurocircuitry underlying motoric impulsivity in rodents performing the 5-choice serial reaction time task (5-CSRTT) will be compared to the DRL schedules since the 5-CSRTT was developed in part to specifically assess specific aspects of impulsivity. The hypothesis will be advanced that the biasing of impulsive behavior toward longer periods of waiting behavior may be a critical feature underlying the positive predictive feature of the DRL 72-s schedule of reinforcement with respect to discrimination of antidepressant drugs from non-antidepressant drugs.

Cognitive dysfunction and depression

Rather than attempting to incorporate as many possible endpoints with face validity for depression into preclinical models/screens for antidepressant drugs, another recently suggested approach is to understand the factors leading into, and maintaining a negative mood state (Holtzheimer and Mayberg, 2011). Increased clinical attention is being paid to the cognitive characteristics of depression involving dysregulation of executive control, memory, temporal perception, affective processing bias, and feedback sensitivity (Bschor et al., 2004; Clark et al., 2009). Not only have the neuroimaging studies of depressed patients highlighted distributed cortical-subcortical circuits underlying depressive symptoms (Price and Drevets, 2010; Drevets et al., 2008; Mayberg, 1997), but aspects of these distributed cortical-subcortical circuits also appear to underpin the dysregulated processing of affectively charged information (Phillips et al., 2003). But rather than a pervasive deficit seen across most cognitive functions for syndromes like schizophrenia, included amongst most salient cognitive deficits in depressed patients may be distortions in managing the affective valence of information processing. These distortions of emotional information processing are intimately related to hopelessness in a manner consistent with earlier notions advanced by Aaron Beck and his colleagues (Beck, 2008; Gvion et al., 2015).
Negative response bias and depression

If emotional information processing is altered in depression, this raises the question as to whether drugs that alter emotional information processing biases in healthy subjects, dysthymic or depressed volunteers may predict antidepressant activity in clinical trials. As reviewed by Pringle and colleagues (Pringle et al., 2011), biases in attention, memory and interpretation have been reported as predicted from Beck’s cognitive theories of depression. These negative biases in depression extend to depressed patients handling of positive or negative emotional expression. In a series of studies pioneered by Phil Cowen and Catherine Harmer, and then extended in an academic/industrial collaboration with P1Vital, this group has produced an Emotional Test Battery that does appear to predict activity of known antidepressants (after a single dose or single week of administration) and that drugs lacking these effects also are not known to produce antidepressant action in the clinic (Harmer et al., 2011).

Modeling depressive cognitive dysfunction and response bias in animals

Depressed subjects are impaired in Go/No-go tasks, as described above, and also exhibit negative cognitive affective biases in such tasks. There are a range of Go/No-go tasks and choice procedures that can be explored for dimensional readouts of executive function. These issues have been examined preclinically. Harding and colleagues trained rats to associate two different auditory cues with different emotional states associated with reward or punishment (Harding et al., 2004). When presented with an ambiguous tone, intermediate to the two that were trained, bias was exhibited toward the tone associated with the negative affective state under circumstances of chronic stress, much as has been shown in depressed humans (Harmer et al., 2009). There have since been many variants of these negative biasing procedures in rodents, notably the Affective Bias Test (Stuart et al., 2013) and in general, antidepressants, predictably, appear to reverse the bias induced by stressors.

Impulsivity and mood disorders
In addition to findings implicating a negative bias of informational processing in mood disorders, there are also reports describing an increase in impulsivity (including motor impulsivity) in mood disorders. While this research has focused more frequently on the clinically obvious increase in impulsivity in patients with bipolar disorders, patients with major depression have also been found to exhibit greater impulsivity than healthy control subjects (Swann et al., 2008). Even euthymic patients with MDD show greater motor impulsivity than healthy control subjects. Recently, these findings have been extended to similar relationships in the children and adolescents with MDD (Peluso et al., 2007).

Akiskal and colleagues (Akiskal et al., 2005) have suggested that approximately 20% of depressed patients may present with an agitated unipolar depression that shares some features of a depressive mixed state with distractibility, racing thoughts, an irritable mood, talkativeness, risky behavior and increased suicidality. Impulsivity appears to discriminate depressed subjects without a history of suicide attempts from those with a positive personal history (Perroud et al., 2011). Thus, increased impulsivity appears to be another aspect of executive function impairment in patients with mood disorders, and especially in those at increased risk for suicide (McCullumsmith et al., 2014; Sanches et al., 2014; Wang et al., 2015; Westheide et al., 2008).

While not being frequently examined on impulsivity in depressed patients per se, antidepressant drugs such as the SSRI sertraline (1S,4S-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine) have been demonstrated to decrease impulsivity (Dunlop et al., 2011). Suicidality may be considered in part a proxy for impulsivity given the relationships between depression, impaired cognition (including ruminative thoughts), hopelessness and suicidal ideation/behavior discussed above. Meta-analyses have consistently found that SSRIs, TCAs, venlafaxine (1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol) (see Fig. 1), and the atypical antipsychotic drug aripiprazole (7-{4-[2,3-dichlorophenyl]-1-piperazinyl}butoxy)-3,4-dihydro-2(1H)-quinolinone) attenuate suicidality (as measured by single items of depression rating scales) with an effect size of 0.21-0.29 (Entsuah et al., 2002; Faries et al., 2000; Hieronymus et al., 2015; Reimherr et al., 2010). This makes the Hamilton...
depression rating scale (HAM-D17) suicide item amongst the 4-5 items most sensitive to pharmacological change. This is a remarkable finding in light of patients with clinically significant suicidal ideation generally being excluded from large multicenter MDD trials conducted by industry sponsors. Like depressed mood, suicidal ideation may show significant improvement within the first several weeks of treatment, unlike the case for a number of neurovegetative symptoms such as early insomnia and appetite (Reimherr et al., 2010; Shelton et al., 2007). Preliminary data for adjunctive treatment with low dose (0.25-2 mg) risperidone (3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]etyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyridol[1,2-a]pyrimidin-4-one also suggested a relatively rapid effect of this 5-HT2A/dopamine D2 receptor antagonist on decreasing suicidality as well as depressed mood within the first few weeks of treatment (Reeves et al., 2008). In an attempt to improve the pharmacological sensitivity of the full-length HAM-D17, addition of the suicidality item to the six-item HAM-D6 results in even greater pharmacological sensitivity than for the Beck subscale (Santen et al., 2008). Thus, a range of antidepressants appear to improve suicidality as assessed using a single suicide item from depression scales (Santen et al., 2008).

The issue of suicidality and antidepressants has been especially controversial dating back to the introduction of black box warnings on suicidality for antidepressant drugs, though a systematic review of clinical and epidemiological studies converge on the finding that antidepressants overall have a beneficial effect on suicidality in depressed patients (Moller, 2006). A large prospective, naturalistic, multicenter study involving 1,014 patients has clearly demonstrated a beneficial effect on suicidal ideation as the improvement of suicidal ideation was reported in 91% of hospitalized inpatients, compared to 3% and 15% of patients with worsening or no change, respectively, in suicidal ideation (Seemüller et al., 2008). Thus, antidepressant drugs have an overwhelming beneficial effect on suicidality from a population perspective. This conclusion is consistent with a web of overlapping relationships between major depression, impulsivity and other executive
dysfunctions, hopelessness and suicidality (Carver et al., 2013; Clark et al., 2011; Joormann and Quinn, 2014; Keilp et al., 2012; Westheide et al., 2008).

**DRL operant schedules and impulsive response bias**

The improvement of response efficiency of rats responding under a differential-reinforcement-of-low rate 72-s (DRL 72-s) schedule has been extensively used as an empirically-derived behavioral screen for antidepressant drugs (O'Donnell et al., 2005). Mice, rats and non-human primates can be trained on DRL schedules resulting in stable baseline behavior on which to explore drug effects. Either water or food can be used to differentially reinforce longer (all interresponse time intervals (IRT)s > 72 s) vs shorter IRTs. When rats are trained to stable baseline of behavior, most antidepressant drug classes, including electroconvulsive shock, have been found to increase the reinforcement rate, decrease response rates and cohesively shift to the right IRT distributions (Fig. 2; Table 1). Most classes of non-antidepressant drugs tested, assuming an adequate background reinforcement rate (baseline reinforcement rate ≥ 7 reinforcers/hour), do not share this common behavioral profile on the DRL 72-s schedule as previously reviewed (O'Donnell et al., 2005). A theoretical basis explaining why DRL behavior appears to predict antidepressant activity was not explicitly evident when this behavioral screen was initially described in the 1980’s by Seiden and colleagues.

Cognition may be a link between DRL behavior and predicting antidepressant-like potential of approved and novel drugs. While drugs may alter different aspects of DRL behavior, including temporal discrimination, an impulsive lever-response bias is another behavioral dimension that may be impacted by antidepressant drugs. When lever pressing on long DRL schedules, if rodents have avoided early bursts of responding during the initial seconds following the previous response, the IRT distribution for individuals or groups of subjects usually peaks around 35-60 seconds. The frequency of longer IRTs progressively decline, though sometimes with another peak with very long pauses > 120 s. The shape of the IRT distribution means that usually less than 15% of total lever presses are followed by availability of
a water (or food) reinforcer. Under control conditions, Fowler and associates have suggested that rats responding on a DRL 72-s schedule locate themselves away from the operant lever and tend to exhibit very little movement (Fowler et al., 2009). Only in the approximately last 8 s prior to a reinforced response or unreinforced response did the rats exhibit an increased amount of horizontal locomotion. In contrast to baseline behavior, psychomotor stimulants like amphetamine (1-phenylpropan-2-amine) increase the response rate, decrease the reinforcement rate and cause a leftward shift in the IRT distribution. This pattern is consistent with expectations for an increased bias toward impulsive responding.

**The 5-choice serial reaction time task (5CSRTT): visual attention and impulsivity**

The 5-CSRTT as employed in preclinical species, such as rodents, is paradigm designed to measure visual attention, motoric impulsivity, and compulsivity; and was originally inspired to study analogous neural processes as those in the human continuous performance task used in healthy volunteers and patients with schizophrenia or ADHD (Robbins, 2002). This task provides a means to study vigilance or sustained attention without potential confounds of impaired motor behavior. Similarly, nose-pokes prior to the presentation of the stimulus starting a new trial is a premature response which may be analogous to leftward-shifted IRTs on a DRL schedule, particularly when omissions in responding during the trial or perseverative responses are not observed. While there are some significant differences between typical 5-CSRT tasks with inter-trial intervals of 5-10 s compared to the DRL 72-s schedule where animals must withhold responding for 72 s following their last response, we will discuss the similarities with respect to psychopharmacology and underlying neurocircuitry between impulsive behavior in the 5-CSRTT and DRL schedules previously suggested by Dalley and colleagues (Dalley et al., 2011).
Pharmacological similarities between DRL 72-s schedule and 5-CSRTT

An important initial psychopharmacological comparison between the DRL 72-s schedule and 5-CSRTT is the systemic administration of channel blocking NMDA receptor antagonists such as dizocilpine or MK-801 (5S,10R)-(+-)5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine) (Table 1). MK-801 results in an increase in premature responses and response omissions on the 5-CSRTT during a time frame where the rats exhibit an increase in locomotor activity (Benn and Robinson, 2014; Higgins et al., 2003; Paine and Carlezon, 2009; Paine et al., 2007; Smith et al., 2011). Local infusion of competitive NMDA receptor antagonists have also been frequently examined to mitigate behavioral confounds of non-competitive channel blocking NMDA receptor antagonists such as prevalent omission in responding during extended periods that animals make no or few responses, this is discussed in the next section on the underlying neuroanatomy of the 5-CSRTT. For DRL 72-s behavior, systemic administration of MK-801 induces a dose-dependent increase in total responses and a leftward shift of the IRT distribution consistent with increased impulsivity (Ardayfio et al., 2008; Hillhouse and Porter, 2014). At high doses, MK-801 can completely suppresses lever pressing probably analogous to increased omissions seen on the 5-CSRTT.

The effects of another channel blocking NMDA receptor antagonist, ketamine (2-(2-chlorophenyl)-2-(methylamino)cyclohexanone), can be at least partially discriminated from MK-801 on both the 5-CSRTT and DRL 72-s behavior. Unlike a stimulant- or psychotomimetic-like action of MK-801 on DRL 72-s behavior, ketamine increases the reinforcement rate, decrease the total response rate and induces a rightward shift of the IRT distribution like antidepressant drugs (Hillhouse and Porter, 2014) (Marek GJ, unpublished observation). In only a single study has ketamine been found to increase premature responding with the 5-CSRTT, and this was in only one of two mouse strains tested (Oliver et al., 2009)). In contrast, systemic administration of ketamine failed to increase premature responding in several studies where MK-801 did increase premature responding (Benn and Robinson, 2014; Smith et al., 2011). In another study, ketamine failed to
increase premature responding as well (Nikiforuk and Popik, 2014). There are several potential explanations for the differential effects of ketamine and MK-801. The first explanation may be the relatively short pharmacological half-life of ketamine in rodent and human studies where a dissociation may be seen with respect to early acute psychomimetic effects and antidepressant-like effects that may be present in humans and rodents after the psychotomimetic effects have resolved.

A second pharmacodynamic-based explanation for the differential effects of ketamine vs MK-801 may be based in the commonly held view that ketamine acts on a number of other pharmacological sites, perhaps including μ-opioid receptors and sigma₁ binding sites (Sanacora and Schatzberg, 2015). At the present time there is widespread agreement that single ketamine doses producing measurable psychomimetic responses also produce an antidepressant-like response in patients beginning several hours after ketamine administration with a duration of up to nearly two weeks (Berman et al., 2000; Iadarola et al., 2015; McGirr et al., 2015). However, it is not clear that any other more selective NMDA receptor antagonist tested in the clinic produces comparable or improved efficacy as ketamine (Sanacora and Schatzberg, 2015). Despite the psychomimetic effects and cognitive impairment that may be produced within the first 30-45 min following ketamine administration, the clinical use of ketamine in depressed patients does appear to decrease suicidality (Ballard et al., 2014; DiazGranados et al., 2010; Price et al., 2014; Zarate et al., 2012).

Striking similarities also exist between the DRL 72-s schedule and the 5-CSRTT with respect to the serotonergic system and serotonin-glutamate interactions. This is most obvious with the widely replicated finding that the 5-HT₂A receptor antagonist M100907 (volinanserin or (R)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol) blocked the impulsive-like NMDA receptor antagonist-induced disruption of 5-CSRTT (Agnoli and Carli, 2012; Carli et al., 2005; Fletcher et al., 2011; Higgins et al., 2003; Mirjana et al., 2004; Pozzi et al., 2010). M100907 similarly attenuates the impulsive-like action of MK-801 on DRL 72-s or DRL 24-s behavior (Ardayfio et al., 2008; Higgins et al., 2003). The 5-HT₂A receptor antagonists M100907 or ketanserin (3-[2-[4-(4-fluorobenzol)pyridin-
1-yl]ethyl]-1H-quinazoline-2,4-dione) alone have been reported to improve impulsive performance of rats trained on the 5-CSRTT (Fletcher et al., 2011; Talpos, 2005). However, selective 5-HT$_{2A}$ receptor antagonists M100907, ketanserin or pipamperone ([1-[4-(4-fluorophenyl)-4-oxobutyl]-4-piperidin-1-ylpiperidine-4-carboxamide) have more consistently been demonstrated to improve impulsivity of rats performing on the DRL 72-s schedule in a dose-dependent fashion (Ardayfio et al., 2008; Balcells-Olivero M et al., 1998; Marek et al., 1989; Marek et al., 2005; Marek and Seiden, 1988). Furthermore, activation of the 5-HT$_{2C}$ receptor acts similarly, and in at least an additive fashion, with blockade of the 5-HT$_{2A}$ receptor on both the 5-CSRTT and DRL 72-s behavior (Agnoli and Carli, 2012; Fletcher et al., 2007; Martin et al., 1998; Navarra, 2008). This functional antagonism between 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors with respect to impulsivity induced by MK-801 was confirmed for the 5-CSRTT and DRL 24-s behavior (Higgins et al., 2003).

With respect to clinical effects, pipamerone is the only 5-HT$_{2A}$ receptor antagonist with at least modest selectivity that has been tested for adjunctive treatment of MDD. In a randomized, multicenter, placebo-controlled trial, dose of pipamperone probably blocking no more than ~60% of brain 5-HT$_{2A}$ receptors appeared to exert an antidepressant effect when added onto citalopram especially during treatment weeks 1-4 (Wade et al., 2011). However, the common pharmacological action shared by approved antidepressants trazodone (2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-1,2,4]triazolo[4,3-a]pyridine-3-one), nefazodone (2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-5-ethyl-4-(2-phenoxyethyl)-1,2,4-triazol-3-one) and mianserin ((±)-2-methyl-1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepine) in addition to the approved atypical antipsychotics aripiprazole, olanzapine (2-methyl-4-(4-methylpiperazin-1-yl)-5H-thieno[3,2-c][1,5]benzodiazepine), risperidone and quetiapine (2-[2-(4-benzo[b][1,4]benzothiazepin-6-yl)piperazin-1-yl]ethoxy]ethanol) is blockade of 5-HT$_{2A}$ receptors. All of these drugs, except risperidone, have been approved by regulatory agencies for either monotherapy or adjunctive
treatment of MDD. However, further evidence is required before definitively concluding that selective blockade of 5-HT$_{2A}$ receptors exerts antidepressant effects in patients with MDD.

Globally increasing 5-HT synaptic availability by administering serotonin transporter (SERT) inhibitors also suppresses premature responses on the 5-CSRTT (Baarendse and Vanderschuren, 2012). While selective serotonin reuptake inhibitors (SSRIs) probably do not as consistently and robustly demonstrate antidepressant responses in rats performing on the DRL 72-s schedule, SSRIs (primarily fluoxetine (N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine)) can exert cohesive rightward shifts in the IRT distribution (increased peak latency) together with increases in the reinforcement rate and decreases in the response rate (Balcells-Olivero et al., 1998; Cousins and Seiden, 2000; Richards et al., 1993b; Sokolowski and Seiden, 1999).

These similar effects of SSRIs on impulsivity for the 5-CSRTT and the DRL 72-s schedule are consistent with the literature on global 5-HT depletions. Earlier findings that global 5-HT depletions with the serotonergic neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) increase impulsivity in rodents measured by increased premature responses on the 5-CSRTT have been translated to humans with 5-HT depletions induced by the dietary tryptophan depletion paradigm in healthy volunteers administered an analogous 4-choice serial reaction time test (Harrison et al., 1997; Winstanley et al., 2004; Worbe et al., 2014). Similarly, global brain 5-HT depletions in rats with intraventricular 5,7-DHT lesions also increases the response rate with a clear leftward shift in the IRT distribution in subjects responding under a DRL 72-s schedule (Jolly et al., 1999). Thus, this similar pattern of changes on presumed motoric impulsivity for the 5-CSRTT and DRL 72-s behavior with serotonergic depletions, global increases in 5-HT availability by SSRIs, 5-HT$_{2A}$ receptor antagonists with or without concurrent NMDA receptor antagonism, and 5-HT$_{2C}$ receptor agonists suggests a central importance for 5-HT in controlling this aspect of impulsivity.

Some but not all drugs acting to inhibit the norepinephrine transporter (NET) display apparent anti-impulsive effects on both the 5-CSRTT and DRL 72-s behavior. Selective NET inhibitors such as
atomoxetine ((3R)-N-methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine) and reboxetine ((2S)-2-
[(S)-(2-ethoxyphenoxy)-phenylmethyl]morpholine), approved for the treatment of attention-deficit
hyperactivity disorder (ADHD) and major depressive disorder (MDD) respectively, both decrease
premature responding of rodents in the 5-CSRTT (Baarendse and Vanderschuren, 2012; Navarra et al.,
2008; Paterson et al., 2011b; Robinson, 2012). In an analogous manner, selective NET inhibitors
reboxetine and (+)-oxaprotiline ((+)-3-(9,10-ethano-9,10-dihydro-9-anthryl)-1-methylamino-2-propanol)
increased the reinforcement rate, decreased the response rate and exerted a cohesive rightward shift in the
IRT distribution of rats responding on a DRL 72-s schedule (Dekeyne et al., 2002; Marek et al., 1988;
Wong et al., 2000). Tricyclic antidepressants such as desipramine (3-(5,6-dihydrobenzo[b][1]benzazepin-
11-yl)-N-methylpropan-1-amine) potently inhibit the NET transporter but also inhibit a range of G-
protein coupled receptors (GCPRs) sharing common transduction pathways such as 5-HT$_{2A/2C}$, $\alpha_1$-
adrenergic, histamine H$_1$, and muscarinic cholinergic receptors. Some TCAs, but not desipramine, also
potently inhibit SERT. Desipramine does suppress premature responses in rats tested on the 5-CSRTT
(Paine et al., 2007). Desipramine, like most TCAs, are amongst the most reliable antidepressant drugs
tested for producing robust antidepressant-like effects (increased reinforcement rate, decreased responses
and a cohesive rightward shift in the IRT distribution) in animals performing on the DRL 72-s schedule
(Ardayfio et al., 2008; Cousins and Seiden, 2000; Hillhouse and Porter, 2014; Marek and Seiden, 1988;
Paterson et al., 2010; Richards et al., 1993a; Richards and Seiden, 1991; Scott-McKean et al., 2008).

In contrast to NET inhibitors and TCAs, compounds inhibiting the NET and dopamine transporter
(DAT) or the DAT alone do not appear to attenuate impulsivity, but rather enhance impulsivity with
respect to both the 5-CSRTT and DRL 72-s behavior. Examination of adequate dose ranges over
adequate 5-CSRTT inter-trial intervals tends to show beneficial effects of methylphenidate (methyl 2-
phenyl-2-piperidin-2-ylacetate) on accuracy or omissions though with increased impulsivity (premature
responses) at higher doses (Navarra et al., 2008; Paine et al., 2007; Paterson et al., 2011a; Robinson,
2012). In rats performing on DRL schedules, methylphenidate also tends to increase response rates and
exert cohesive leftward shifts in IRT distributions especially at higher doses (Andrzejewski et al., 2014; Orduña et al., 2009; Seiden et al., 1979). Antidepressants thought to primarily act as NET/DAT inhibitors such as nomifensine (2-methyl-4-phenyl-3,4-dihydro-1H-isoquinolin-8-amine) and bupropion (2-(tert-butylamino)-1-(3-chlorophenyl)propan-1-one) test as “false negatives” on the DRL 72-s schedule and increase the response rate with a cohesive leftward shift appearing positively biased towards greater impulsivity (Dekeyne et al., 2002; O'Donnell and Seiden, 1983; Paterson et al., 2011a; Seiden et al., 1985). The similar cohesive leftward shift of the IRT distribution by the DAT inhibitor GBR12909 (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine; dihydrochloride) suggests that DAT inhibition, unlike NET inhibition, is responsible for the apparent increase in impulsivity seen with either methylphenidate, bupropion or nomifensine (Paterson et al., 2011a).

Amphetamine appears to increase impulsivity when tested in rodents both for the 5-CSRTT and DRL behavior, a result not surprising considering the apparent role played by dopamine for NET/DAT inhibitors like methylphenidate, nomifensine and bupropion. Dopamine release in the nucleus accumbens appears sufficient for these effects given that amphetamine increases premature responses on the rat 5-CSRTT regardless of a dorsal noradrenergic bundle lesion status, sham or active (Cole and Robbins, 1987). Both baseline premature responses and amphetamine-induced premature responses were attenuated by 6-hydroxydopamine (6-OHDA)-induced lesions of the nucleus accumbens (Cole and Robbins, 1989). Independent laboratories have replicated amphetamine-induced impulsivity for the 5-CSRTT (Baarendse and Vanderschuren, 2012; Paterson et al., 2011b; Pattij et al., 2007). For DRL 72-s behavior, amphetamine-induced increases in impulsivity have been suggested by increased response rates and cohesive leftward shift in the IRT distribution, including decreased peak latency (Balcells-Olivero et al., 1998; Fowler et al., 2009; Paterson et al., 2011a).

These observations with amphetamine are important with respect to predictions for antidepressant efficacy when moving from rodent DRL 72-s behavior to the clinical treatment of patients with MDD. Despite anecdotal evidence for antidepressant effects of amphetamine, double-blind, placebo-controlled
studies with amphetamine and other stimulants generally have been negative (Abbasowa et al., 2013; Satel and Nelson, 1989). The primary patient population benefiting from amphetamine appears to be a population of medically ill subjects with depressive symptoms. This lack of efficacy for amphetamine in controlled randomized clinical studies of patients with MDD may seem surprising given the interest in anhedonia as a model for depression; and the relationship of anhedonia to the dopamine system. However, despite numerous efforts by industry sponsors, clinical testing of new chemical entities possessing dopamine transporter blockade in addition to SERT and NET inhibition has not resulted in any therapeutic advances beyond that seen for SSRIs and SNRIs (Bhagwagar et al., 2015; Learned et al., 2012; Tran et al., 2012). The reason for these relative failures is not clear although one speculation consistent with the primary thesis of this review is that clinically useful antidepressants may need to improve mood and decrease impulsivity (and indirectly decrease suicidality) on a sustained basis. Nevertheless, rigorous testing of amphetamine and other stimulants including triple reuptake inhibitors imply that simply enhancing synaptic availability of dopamine does not result in therapeutic effects for depression like those seen over 10-30 years of clinical experience with SSRIs or SNRIs.

Studies examining specific subtypes or classes of adrenergic receptors also generally provide convergent evidence for the hypothesis that action or motor impulsivity plays a critical role in mediating drug effects for the 5-CSRTT and the DRL 72-s schedule. The β2-adrenergic agonist clenbuterol (1-(4-amino-3,5-dichlorophenyl)-2-(tert-butylamino)ethanol) suppressed premature responses in rats performing on the 5-CSRTT (Pattij et al., 2012). A series of DRL 72-s experiments clearly demonstrated that clenbuterol and another β2-adrenergic receptor agonist salbutamol (4-[2-(tert-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol) increased the reinforcement rate and decreased the response rate similar to known antidepressants (Dunn et al., 1993; O'Donnell, 1987; 1990; Zhang et al., 2003). Clenbuterol and salbutamol also appeared to shift the impulsivity bias of the rats lever pressing on the DRL 72-s schedule by a cohesive rightward shift towards longer IRTs (Dunn et al., 1993; O'Donnell, 1987; 1990; Zhang et al., 2003). While no large placebo-controlled multicenter studies of β2-adrenergic
agonists in patients have been conducted, several preliminary controlled trials suggest that i.v. infusion of salbutamol or oral administration of clenbuterol produces relatively rapid antidepressant responses in at least a subpopulation of depressed patients (Lecrubier et al., 1980; Simon et al., 1984).

Another interesting candidate GPCR to explore is the $\alpha_1$-adrenergic receptor given close neuroanatomical and functional overlap with 5-HT$_2A$ receptors, and also given that most TCAs potently block this site. The prototypical $\alpha_1$-adrenergic receptor antagonist prazosin does not have an effect by itself on premature responses in the rat 5-CSRTT (Koskinen et al., 2003; Liu et al., 2009). Analogously, prazosin ([4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]-(furan-2-yl)methanone) and several non-selective $\alpha$-adrenergic receptor antagonists did not increase the reinforcement rate or exert a cohesive rightward shift of the IRT distribution in rats performing on a DRL 72-s schedule (Marek et al., 1989; Marek and Seiden, 1988).

Of further interest, $\alpha_2$-adrenergic receptors appear to play a critical role in mediating anti-impulsive effects of the TCA nortriptyline (3-(5,6-dihydrodibenzo[2,1-b:2',1'-f][7]annulen-11-ylidene)-N-methylpropan-1-amine) or desipramine on an auditory sustained attention test (Roychowdhury et al., 2012) or DRL 72-s behavior (Zhang et al., 2008). Consistent with these results, the $\alpha_2$-adrenergic receptor agonist guanfacine (N-(diaminomethylidene)-2-(2,6-dichlorophenyl)acetamide) suppressed, while the $\alpha_2$-adrenergic receptor antagonist yohimbine (methyl (1S,15R,18S,19R,20S)-18-hydroxy-1,3,11,12,14,15,16,17,18,19,20,21-dodecahydroyohimban-19-carboxylate) increased 5-CSRTT premature responses in rats (Fernando et al., 2011; Pillidge et al., 2014; Sun et al., 2010). Thus, while more work remains to clarify the role of specific $\alpha_1$-adrenergic and $\alpha_2$-adrenergic subtypes on 5-CSRTT and DRL 72-s behavior, converging pharmacological evidence for NET inhibitors, $\beta_2$-adrenergic receptor agonists, $\alpha_1$-adrenergic receptor antagonists and $\alpha_2$-adrenergic receptor agonists support the hypothesis that motoric impulsivity is an important aspect for both behavioral paradigms.
In addition to MK-801 and other NMDA receptor antagonists, the muscarinic cholinergic receptor antagonist scopolamine (6,7 epoxytropane tropate) is frequently used both in preclinical and clinical studies as a pharmacological perturbation impairing cognition. While a range of scopolamine effects are seen in rats performing under particular 5-CSRTT conditions with respect to accuracy and omissions, premature responses are increased (de Bruin et al., 2006; Jones and Higgins, 1995; Shannon and Eberle, 2006). While scopolamine induces robust effects on DRL 72-s behavior that may largely reflect a disruption of stimulus control, the decreased reinforcement rate, increased response rate and the leftward shift in the IRT distribution is also compatible with increased motoric impulsivity (Jayarajan et al., 2013). Thus, the similar valence of effects for NMDA receptor antagonists like MK-801, psychomotor stimulants, and scopolamine together with analogous directional effects for a range of serotonergic and noradrenergic drugs (many of which antidepressant drugs) are consistent with the hypothesis that an overlapping pharmacology and neurocircuitry may mediate biasing of motor impulsivity as a key driver for premature responses on the 5-CSRTT and DRL 72-s behavior. These preclinical effects of scopolamine do appear contradictory to the major thesis advanced in this review since scopolamine appears to exert antidepressant effects in patients with MDD and bipolar depression from double-blinded, placebo-controlled trials (Drevets and Furey, 2010; Furey and Drevets, 2006). The reason for this apparent contradictory finding remains to be determined. Further work examining scopolamine effects with longer pretreatment intervals would be one important factor to examine in order to test for the potential dissociation of disruptive acute effects and downstream effects with a slower onset. Potential ancillary pharmacology of scopolamine may also be a factor in its putative antidepressant efficacy.

One issue that should be highlighted for the DRL 72-s schedule and 5-CSRTT with respect to measuring modulation of motoric impulsivity and predicting clinical antidepressant action is that these modulatory effects on impulsivity are seen following a single dose of drug. Furthermore, these antidepressant-like effects of drugs on the DRL 72-s schedule do not necessarily increase in magnitude with subchronic administration with a current relatively small body of work directed at answering this
question. The antidepressant-like effects of the TCA imipramine (3-(5,6-dihydrobenzo[b][1]benzazepin-11-yl)-N,N-dimethylpropan-1-amine) on DRL 18-s behavior appeared to be enhanced by subchronic treatment at a higher (10 mg/kg), but not a lower (5 mg/kg) dose (McGuire and Seiden, 1980). Tachyphylaxis appeared to develop within a few days for the antidepressant-like effects of clenbuterol during subchronic treatment (O'Donnell, 1990). However, the observations that acute single doses of antidepressant drugs may alter emotional information processing in human subjects as a translational paradigm for predicting antidepressant activity for new clinical entities (Harmer et al., 2011) appears to parallel the rodent DRL antidepressant screening paradigm. Presumably, the DRL 72-s schedule is measuring the acute antidepressant treatment effects in a subset of the circuitry that must be modified in order to begin to see a meaningful clinical response within 2-6 weeks of daily administration. However, the DRL 72-s schedule also appears capable of detecting an acute antidepressant effect of ketamine that may be more similar to the clinical time course in patients with MDD (Hillhouse and Porter, 2014).

Thus, drugs acting at a number of biologically salient and clinically validated targets (NMDA receptors, 5-HT2A receptors, serotonin synthesis/release, and NET) appear to similarly attenuate or enhance impulsivity on the 5-CSRTT and the DRL 72-s behavior. These results do not appear surprising given that withholding of inappropriate responding is at least a component of both tasks. These pharmacological similarities among the 5-CSRTT and the DRL-72 are further supported by other procedures which measure response inhibition, such as response-duration differentiation in which aspects of impulsivity are clearly produced by an NMDA antagonist and d-amphetamine, and reduced by antidepressant administration, including bupropion and nomifensine (Hudzik and McMillan, 1994a; b).

Candidate circuitry sharing similar influences on impulsivity/executive function

The prefrontal cortex (PFC) and its direct and indirect projections may mediate impulsive responding for both DRL behavior and the 5-CSRTT. The rodent prefrontal cortex is divided into both the medial PFC (mPFC), the orbital PFC, and the more lateral agranular insular cortex. These areas are
further divided into smaller areas defined by cytoarchitectonic features and neural connectivity with functional macocircuits including thalamo-cortico-striatal loops (Heidbreder and Groenewegen, 2003).

For the purposes of this review, we will focus upon distinctions between the dorsomedial aspect of the mPFC (including the dorsal anterior cingulate cortex, dACC; the dorsal aspect of the prelimbic cortex (PrL) and the ventromedial aspect of the mPFC (including the ventral PrL, the infralimbic cortex (IL), and the medial orbital cortical areas). Three different types of thalamic afferents project to these mPFC regions, with discrete topological relationships including the midline and intralaminar thalamic nuclei, the mediodorsal nucleus of the thalamus and the anterior thalamic nuclei, and these bidirectional thalamocortical connections are thought to play a major role in executive functions and cognition involving the PFC (Bradfield et al., 2013; Mitchell et al., 2014; Saalmann, 2014). Both the midline thalamic nuclei and the anterior thalamic nuclei may relay cognition/executive function-related information between the mPFC and the hippocampal formation (Cassel et al., 2013; Prasad and Chudasama, 2013; Vertes et al., 2015). The prefrontal cortex (and the thalamus) is topographically connected to the dorsal striatum and the ventral striatum (nucleus accumbens core and shell) with return of striatal input to the cortex via the thalamus (Heidbreder and Groenewegen, 2003). These circuits are then reinforced by the modulatory action of brainstem monoamines (dopamine, serotonin, norepinephrine) which project diffusely throughout the cortical mantle as well as subcortical regions.

**Comparison of neurocircuity underlying 5-CSRTT and DRL behavior**

Similar, at least partially, overlapping neurocircuitry appears to underpin the control of impulsivity on the DRL 72-s schedule and the 5-CSRTT (Table 2). As discussed previously, global serotonergic lesions using relatively selective neurotoxins have been found to enhance motoric impulsivity for both the 5-CSRTT and DRL behavior (Fletcher, 1995; Harrison et al., 1997; Jolly et al., 1999). The significance of this commonality is underscored by a growing body of evidence supporting the hypothesis that impulsivity in not a unitary construct. With respect to global 5-HT lesions, neither impulsive choice quantified by a delay-discounting model nor stopping a prepotent response for the stop-
signal reaction time task (SSRT) were impacted by 90% reductions of global forebrain 5-HT by intracerebroventricular 5,7-dihydroxytryptamine (5,7-DHT) (Eagle et al., 2008; Winstanley et al., 2004). With respect to DRL behavior and the 5-CSRTT, decreasing 5-HT locally in the cortex by more than 80% did not alter impulsivity for either the 5-CSRTT or shorter DRL 20-s or 40-s schedules (Fletcher et al., 2009). However, Fletcher and colleagues did report one difference between the 5-CSRTT and DRL 20-s behavior as local 5,7-DHT infusions into the nucleus accumbens increased impulsive behavior for the DRL schedule, but not the 5-CSRTT. Nevertheless, the general pattern of results with global and local 5-HT depletions seems consistent with the pharmacological similarities between impulsivity measured by the DRL behavior and the 5-CSRTT.

Animals examined months following limbic seizures induced by lithium and pilocarpine ((3S,4R)-3-ethyl-4-[(3-methylimidazol-4-yl)methyl]oxolan-2-one) appear to share at least a trend towards increased impulsivity. Two months following lithium-pilocarpine-induced seizures these rats, unlike controls, failed to acquire DRL 6-s or DRL 12-s behavior with responding biased toward short IRTs <3 s (Harrigan et al., 1990). These lithium-pilocarpine treated rats exhibited “extreme necrosis in the amygdal, pyriform-entorhinal cortices and the dorsomedial and lateral thalamic nucleiar groups” as previously described by the senior author (Persinger et al., 1988). More recently, the behavior of rats with limbic seizures following lithium-pilocarpine treatment was examined using the 5-CSRTT several months following motor seizures. These rats showed trends toward an increased percentage of premature responses that were correlated negatively with neuronal density in hippocampal field CA3 and the infralimbic cortex (Faure et al., 2014). Thus, while rats performing a DRL schedule were more severely impaired than those engaged on a 5-CSRTT, the shared valence of effects with this manipulation is in keeping with anatomical results described below.

Shared neurocircuitry underlying impulsivity on DRL schedules and the 5-CSRTT is also supported by results of gestational methylazoxymethanol acetate (e.g., MAM) ((Z)-hydroxymethylimino- methyl-oxidoazanium) treatment. Treatment of pregnant female rats with MAM on gestational day 17
results in adult offspring with a range of thalamocortical histopathological alternations, prefrontal cortical and striatal neuron electrophysiological changes, and increased sensitivity to amphetamine with striking congruence to features observed in patients with schizophrenia (Lodge and Grace, 2009; Moore et al., 2006). A similar course of gestational MAM treatment in rats has also been to increase impulsivity in adult offspring trained on DRL 20-s behavior: exemplified decreased reinforcement rate, modestly increased response rate, decreased efficiency, and approximately a 5 s shift towards short IRTs as calculated by the mean IRT (Featherstone et al., 2006). In the latter study, surprisingly, the only effect of gestational MAM treatment in adult rat offspring was a trend towards increased premature responses on the 5-CSRTT. A rodent MRI study has reported significant parallel findings in juvenile and adult offspring of MAM treated dams to the structural findings in adults with schizophrenia such as increased ventricle size and reduced hippocampal, cerebellum and whole brain volumes along with evidence of decreased connectivity from major fiber tracts in the forebrain (Chin et al., 2010). Unknown however, is what regions altered by this developmental insult are responsible for the apparent increase in motoric impulsivity as a range of cortical regions (mPF, orbital PFC, parietal, hippocampal) and subcortical regions (dorsal striatum) from offspring of MAM-treated dams show tissue weight reductions. The significance of these results for the DRL 72-s schedule as a screen for antidepressant drugs is that suicide victims dying with major depressive disorder also exhibit decreases in lateral ventricular size in addition to decreases in the prefrontal cortical thickness and hippocampal volume (Koolschijn et al., 2009; McKinnon et al., 2009).

The 5-CSRTT has been characterized from a neuroanatomical perspective with significantly greater granularity than most behavioral tasks, including DRL behavior. Both tasks appear to require the prefrontal cortex (PFC) in keeping with a close relationship between a range of executive functions and different anatomical and functional regions of the PFC. Several excitotoxic lesion studies demonstrated the increased impulsive (premature) responding in the 5-CSRTT following ventromedial PFC (e.g., infralimbic cortex, IL) or anterior cingulate cortex lesions (Chudasama et al., 2003a; Chudasama et al.,
2003b; Muir et al., 1996). In contrast, lesions restricted to the dorsal anterior cingulate cortex impaired discriminative accuracy while lesions largely restricted to the dorsal medial prefrontal cortex (e.g., prelimbic cortex, PL) also were impaired in choice accuracy in contrast to increases in perseverative responding with orbitofrontal lesions (Chudasama et al., 2003b; Muir et al., 1996). Converging evidence for the role played by the infralimbic cortex in suppressing premature responses with the 5-CSRTT are direct regional infusion studies with 5-HT$_{2A}$ receptor antagonists, 5-HT$_{1A}$ receptor agonists, and the competitive NMDA receptor antagonist R-CPP (3-((R)-2-Carboxypiperazin-4-yl)-propyl-1-phosphonic acid) (Carli et al., 2005; Muir et al., 1996; Winstanley et al., 2004). In contrast to the increase in premature responses with intra-IL cortical local administration, infusion of R-CPP into the prelimbic cortex directly dorsal to the IL cortex impaired accuracy and increased omissions (Murphy et al., 2005). Thus, the infralimbic cortex appears to be an especially important region regulating motor impulsivity as measured with the 5-CSRTT.

The only published DRL neurocircuitry study where the majority of the IL and PRL cortices where destroyed with an excitotoxic lesion found that compared to sham-treated mice, the mice with lesions exhibited a flattened, wider IRT distribution (Cho and Jeantet, 2010). Mixed results were observed in lesion studies examining acquisition of DRL behavior. Several reported either a decreased reinforcement rate coupled with increased response rate while another demonstrated an increase in very short IRTs (Nalwa and Rao, 1985; Numan et al., 1975). However, several other studies failed to demonstrate an effect of medial frontal cortex lesions, though in one study the lesion may have spared the IL (Finger et al., 1987; Kolb et al., 1974). Several other studies with mPFC lesions that clearly appeared to spare the infralimbic cortex did not have an effect on DRL responding (Neill, 1976; Neill et al., 1974). Similar to experiments with the rodent 5-CSRTT, orbital frontal lesions may produce perseverative responding in rats on a DRL 20-s schedule (Kolb et al., 1974). Thus, further fine-grained anatomical work in light of modern neuroanatomical knowledge is clearly required, especially since dissociations in
the mediation of different executive functions have been observed across distinct regions of the prefrontal cortex in rodents on the 5-CSRTT as described earlier.

The hippocampal formation appears involved in suppressing premature impulsive responding. The more extensive body of evidence exists for the DRL schedule (compared to the 5-CSRTT) where studies testing DRL neurocircuitry reviewed elsewhere generally have found large increases in responding, especially following aspiration or electrolytic lesions (Gray and McNaughton, 1983). Cytotoxic hippocampal lesions in both rats and mice, particularly when involving both the ventral and dorsal hippocampus or complete CA1/CA3/dentate gyrus involvement, also increased DRL response rates, decreased reinforcement rates, decreased efficiency and resulted in a leftward IRT distribution shift (Cho and Jeantet, 2010; Reisel et al., 2005; Sinden et al., 1986). With regard to the 5-CSRTT, only excitotoxic lesions of the rat ventral hippocampus increased premature (impulsive) responses while no effect was observed with dorsal hippocampus lesions (Abela et al., 2013). Not surprisingly, the SSRI escitalopram reduced the number of premature responses observed after the ventral hippocampal lesion whereas a DAT inhibitor GBR 12909 was without effect (Abela et al., 2013). In an additional refutation to a unitary impulsivity hypothesis, these ventral hippocampal lesions did not affect reversal learning where the rats are required to inhibit previously reinforced responses. The influence of the ventral hippocampus was replicated and extended to suggest that obligate functional interactions of the infralimbic cortex and the ventral hippocampus exists by making disconnection lesions of the IL and ventral hippocampus (VH) on opposing hemispheric sides (e.g., left IL and right VH lesions) in contrast to ipsilateral lesions of both structures (Chudasama et al., 2012). The primary observation was that while both ipsilateral combined lesions of the IL and the VH and the disconnection lesions increased premature responses 2 weeks following the surgery, increased responses were only observed for the disconnection lesions (left IL and right VH lesions) 2 months following the surgery. Thus, both the infralimbic cortex and the ventral hippocampus appear to work together in modulating “waiting behavior” before making an appropriately timed response to obtain a reward.
The thalamus may provide an appropriate neuroanatomical substrate for indirect interactions between the infralimbic cortex and the ventral hippocampus. The reunions nucleus is one of the midline and intralaminar thalamic nuclei (e.g., “non-specific” thalamic afferents) having neurons that either project to the mPFC (including the infralimbic cortex) or/and the hippocampal formation (including the CA1 field, entorhinal cortex, subiculum) in a bidirectional manner (Cassel et al., 2013). With respect to the rat 5-CSRTT, local neurotoxic lesions in the reunions nucleus increased premature responses while also decreasing perseverative responses through 2 months following the surgery (Prasad et al., 2012). Lesions of the medial dorsal thalamic nucleus that spare the reunions nucleus have also been found to increase premature responding with the rat 5-CSRTT (Chudasama and Muir, 2001). While no studies have been performed with selective midline or intralaminar thalamic nuclei in rats and the DRL, human subjects with Korsakoff’s syndrome have been found to exhibit disruptions of DRL performance. Namely, Korsakoff patients increase response rates with a left-shifted IRT distribution as a function of increasing the schedule time requirement from DRL 3-s up to the highest schedule tested, DRL 18-s behavior (Oscar-Berman et al., 1982). The subjects with Korsakoff’s syndrome appeared more impulsive when compared to alcoholic subjects with Korsakoff’s syndrome or healthy subjects. Selective alterations in appropriate midline and intralaminar thalamic nuclei or appropriate segments of the medial dorsal thalamic nucleus in rodent or non-human primate DRL studies is required to understand whether the damage in the medial thalamus (including midline thalamic nuclei), mammillary bodies or corpus callosum is responsible for motoric impulsivity present in subjects with Korsakoff’s syndrome (Nardone et al., 2013; Pitel et al., 2012).

Initial similarities have emerged for lesion studies with the 5-CSRTT and more limited work on DRL schedules with respect to the ventral striatum or nucleus accumbens. While neither nucleus accumbens core or shell lesions increased 5-CSRTT premature responses, a differential effect of these lesions was seen on the impulsivity-inducing effect of d-amphetamine (Murphy et al., 2008). Namely, the core lesions further increased premature responses induced by d-amphetamine while the shell lesions
attenuated the amphetamine-induced increase in premature responses. Acute deactivation experiments with the GABA_A receptor agonist muscimol (5-(aminomethyl)-1,2-oxazol-3-one) also reveal distinct profiles with either nucleus accumbens shell or core inactivation (Feja et al., 2014). Acute inactivation of the shell increases premature responses while acute inactivation of the nucleus accumbens core results in a large increase in omissions.

Other pharmacological manipulations also suggest differential effects of the nucleus accumbens shell and core regions on premature responses with the 5-CSRTT. For example, the dopamine D_2 receptor antagonist eticlopride (5-chloro-3-ethyl-N-[(2S)-1-ethylpyrrolidin-2-yl]methyl]-2-hydroxy-6-methoxybenzamide) decreases amphetamine-induced impulsivity when the antagonist is infused into the core, but increases amphetamine-induced impulsivity when the antagonist is infused into the shell (Pattij et al., 2007). In an analogous manner, the dopamine D_{2/3} receptor agonist quinpirole (4aR,8aR)-5-propyl-1,4,4a,6,7,8,8a,9-octahydropyrazolo[3,4-g]quinoline increased premature responding when infused into the nucleus accumbens core in a subpopulation of highly impulsive Lister hooded rats, while no effect was observed for infusions into the shell region (Pattij et al., 2007).

A range of 5-CSRTT studies employing excitotoxic lesions, acute inactivation and local infusion methods also support functional interactions between the prefrontal cortex and the nucleus accumbens with respect to motoric impulsivity. For example, both bilateral nucleus accumbens core and mPFC-nucleus accumbens core disconnection lesions (unilateral lesions on the opposite side of the brain) resulted in increased premature responses only after a failed trial, but not a correct trial (Christakou, 2004). Also analogous to effects of bilateral inactivation in either the ventral mPFC or the nucleus accumbens shell, a disconnection inactivation of the ventral mPFC and the contralateral nucleus accumbens shell, but not the core, increased premature responses (Feja and Koch, 2014). Finally, infusion of the dopamine D_{2/3} receptor antagonist sulpiride (N-[(1-ethylpyrrolidin-2-yl)methyl]-2-methoxy-5-sulfamoylbenzamide) into the nucleus accumbens core suppressed the increased impulsivity observed for a mPFC lesion including the anterior cingulate, prelimbic, and infralimbic cortex (Pezze et
al., 2008). Thus, this and more recent converging evidence supports important functional relationships between the ventral PFC and the nucleus accumbens in mediating impulsivity on the 5-CSRTT (Donnelly et al., 2014). While fewer experiments have examined the nucleus accumbens in mediating DRL behavior, these few studies are consistent with findings in the 5-CSRTT literature. Thus, bilateral nucleus accumbens lesions have been demonstrated to increase impulsivity in rats performing under a DRL 20-s schedule, while also attenuating the impulsive profile of amphetamine on this schedule (Reading and Dunnett, 1995). Differential effects for nucleus accumbens core and shell lesions are also observed for DRL behavior. Excitotoxic lesions of the nucleus accumbens core, but not the shell region, increased responding of rats on a DRL 18-s schedule while only a trend was observed for these same rats performing under a DRL 12-s schedule (Pothuizen et al., 2005). The limited exploration of nucleus accumbens involvement for DRL behavior with respect to impulsivity is generally consistent with the more robust literature with the 5-CSRTT.

While the neurocircuitry underlying impulsivity with the 5-CSRTT has been explored to a greater degree than apparent impulsivity with DRL schedules (increased response rate with leftward shifted IRTs), there appears to be a striking correspondence regarding PFC-striato-thalamic-hippocamal and serotonergic circuitry mediating these two distinct operant paradigms.

A single study has examined DRL behavior following olfactory bulb removal in rodents. This study is intriguing given (1) the generally high selectivity and sensitivity of the olfactory bulbectomy paradigm as a model for testing new chemical entities a number of commonly used antidepressant screens and (2) the wide constellation of behavioral, endocrine and immunological observations in olfactory bulbectomized rats resembling patients with major depressive disorder (Kelly et al., 1997; Song and Leonard, 2005). Olfactory bulbectomized rats responded more frequently and with a lower efficiency on a DRL 20-s schedule than control rats (Thorne et al., 1976). This result is not surprising given relationships between motoric impulsivity and aggression and that in early years of this model, muricide was an important endpoint employed by many investigators.
Conclusions

DRL 72-s behavior, while a complex operant paradigm, provides an opportunity to observe drug-induced changes on a dimension of motoric impulsivity related to inhibition of inappropriate responses (e.g., responses prior to the scheduled defined 72-s waiting requirement) as a key executive function. Both the psychopharmacology and underlying neurocircuitry that appear to be shared between the 5-CSRTT and DRL schedules emphasize the importance of impulsivity for DRL schedules. This raises the hypothesis that the demonstrated validity of DRL 72-s behavior with respect to accurately predicting antidepressant activity in the clinic may in part reflect the frank improvement in certain cognitive functions that may be disturbed in depressed patients. This clinical correlate may be most apparent when considering agitated, impulsive depressed patients. This improvement in emotional response bias or impulsive response bias of patients with mood disorders may be a relatively early event occurring on a time frame preceding lifting of the depressed mood and improvement of suicidality. Thus, the DRL 72-s schedule may be more than just an empirical predictor of antidepressant drugs. The DRL 72-s schedule may also be of heuristic interest with respect to developing new and improved preclinical antidepressant drug screens/models in this age of personalized medicine.

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Figure Legends

**Fig. 1.** Correlations of antidepressant drug effect size for individual items of the HAMD-17 item depression scale derived from published meta-analyses and reviews. The top graph shows the correlation between the effect sizes for SSRIs (Hieronymus et al., 2015) versus tricyclic antidepressants (TCAs) (Faries et al., 2000). For this correlation, r^2=0.051 with p=0.0005. The lower graph shows the correlation between the effect sizes for SSRIs (Hieronymus et al., 2015) versus the SNRI venlafaxine (Entsuah et al., 2002). For this correlation, r^2=0.778 with p<0.0001. The suicidal ideation item, one of the top five pharmacologically sensitive items, is demarcated for number 3. The other items are: (1) mood; (2) guilt; (4) early insomnia; (5) middle insomnia; (6) late insomnia; (7) work/activities; (8) retardation; (9) agitation; (10) psychic anxiety; (11) somatic anxiety; (12) gastrointestinal somatic symptoms; (13) general somatic symptoms; (14) genital symptoms; (15) hypochondriasis; (16) loss of weight; (17) insight.

**Fig. 2.** Antidepressant-like effects of drugs in rats performing on the DRL 72-s schedule exemplified by the tricyclic antidepressant desipramine. Top Graph: The dose-dependent increase (0.625-10 mg/kg, ip) in the reinforcement rate for a group of 8 male Sprague-Dawley rats is shown in the top graph expressed as the mean + SEM reinforcers obtained during a 60 min behavioral session. The middle graph displays the dose-dependent decrease in the total responses relationship for desipramine in this same group of rats. The increase in the reinforcement rate and decrease in response rate is characteristic of most antidepressant drugs including electroconvulsive shock. * p<0.05; ** p<0.01; *** p<0.001. C, displays the inter-response time (IRT) distribution (measured in s) derived from the entire group of rats shown above. The cohesive rightward shift in the peak of IRTs close to the reinforcement time requirement (72
s) is characteristic of antidepressant drugs and may reflect, at least in part, an effect of antidepressant drugs on motoric impulsivity.
Table 1. Psychopharmacological modulation of impulsivity for 5-CSRTT<sup>a</sup> and DRL schedules<sup>b</sup>.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>5-CSRTT&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DRL&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Clinical Antidepressant Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NET inhibitors</td>
<td>↓ [1-4]</td>
<td>↓ [5-7]</td>
<td>Approved antidepressant</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>↓ [8]</td>
<td>↓ [9-15]</td>
<td>Approved antidepressants</td>
</tr>
<tr>
<td>SERT inhibitors</td>
<td>↓ [4]</td>
<td>↓ [13,16-18]</td>
<td>Approved antidepressants</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2A&lt;/sub&gt; receptor antagonists</td>
<td>↓ [19-24]</td>
<td>↓ [25-29]</td>
<td>Additional testing needed &lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2C&lt;/sub&gt; receptor agonists</td>
<td>↓ [30,31,24]</td>
<td>↓ [32]</td>
<td>Not tested</td>
</tr>
<tr>
<td>NMDA antagonist MK-801</td>
<td>↑ [8,19,33-35]</td>
<td>↑ [14,15]</td>
<td>MK-801 not tested in humans</td>
</tr>
<tr>
<td>ketamine</td>
<td>↔ [34-37]</td>
<td>↓ [15,38]</td>
<td>Positive DB, PC trials &lt;sup&gt;”&lt;/sup&gt;[39-41]</td>
</tr>
<tr>
<td>DAT/NET inhibitors</td>
<td>↑ [1,2,8,42]</td>
<td>↑ [9,7,43-45]</td>
<td>Approved antidepressants &lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>amphetamine</td>
<td>↑ [2,4,45-47]</td>
<td>↑ [12,17,49]</td>
<td>Negative DB, PC trials &lt;sup&gt;50,51&lt;/sup&gt;</td>
</tr>
<tr>
<td>α&lt;sub&gt;1&lt;/sub&gt;-adrenergic receptor antagonists</td>
<td>↔ [52,53]</td>
<td>↔ [5,25]</td>
<td>Not tested</td>
</tr>
<tr>
<td>α&lt;sub&gt;2&lt;/sub&gt;-adrenergic receptor agonism</td>
<td>↓ [54-56]</td>
<td>↓ [57]</td>
<td>Not tested</td>
</tr>
<tr>
<td>β&lt;sub&gt;2&lt;/sub&gt;-adrenergic receptor agonism</td>
<td>↓ [58]</td>
<td>↓ [59-62]</td>
<td>Positive comparator trials &lt;sup&gt;63,64&lt;/sup&gt;</td>
</tr>
<tr>
<td>scopolamine</td>
<td>↑ [65-67]</td>
<td>↑ [68]</td>
<td>Positive DB, PC trials &lt;sup&gt;69,70&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Impulsivity on the 5-CSRTT is defined by an increase in premature responses

<sup>b</sup> Impulsivity on DRL schedules is defined by a pattern of responding including a decreased reinforcement rate, increased response rate and a cohesive leftward shift of the IRT distribution

<sup>c</sup> Pipamperone is the most selective drug tested in a randomized multicenter, placebo-controlled trial (Wade et al., 2011). However, the common pharmacological action shared by approved antidepressants trazodone and mianserin and approved atypical antipsychotics aripiprazole, olanzapine, risperidone and quetiapine is blockade of 5-HT<sub>2A</sub> receptors.

<sup>d</sup> double-blind (DB) and placebo-controlled (PC)

<sup>e</sup> Bupropion and nomifensine were both approved by regulators for the treatment of MDD but methylphenidate and other stimulants have generally not been found to exert antidepressant effects in randomized placebo-controlled trials (Abbasowa et al., 2013)

Table 2. Effects of lesions on impulsivity with 5-CSRTT and DRL behavior

<table>
<thead>
<tr>
<th>Lesion site/method</th>
<th>5-CSRTT</th>
<th>DRL behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,7-DHT (ivt) lesion of serotoninergic neurons</td>
<td>↑ [1,2]</td>
<td>↑ [3-5]</td>
</tr>
<tr>
<td>mPFC lesion (including infralimbic cortex)</td>
<td>↑ [7-9, 15]</td>
<td>↑ [10]</td>
</tr>
<tr>
<td>hippocampus lesions</td>
<td>↑ [11, 12, 15]</td>
<td>↑ [10, 13,14]</td>
</tr>
<tr>
<td>MAM gestational day 17 genetic lesions</td>
<td>↑ [6]</td>
<td>↑ [6]</td>
</tr>
<tr>
<td>Medial thalamic lesions</td>
<td>↑ [16,17]</td>
<td>↑ [18-20]</td>
</tr>
<tr>
<td>Ventral striatum lesions (n. accumbens core)</td>
<td>↑ [21,22]</td>
<td>↑ [23,24]</td>
</tr>
<tr>
<td>Lithium/pilocarpine induced lesions</td>
<td>↑ ↔ [25]</td>
<td>↑ [26]</td>
</tr>
</tbody>
</table>

HAMD-17 individual item correlation

Fig. 1
Fig 2